REMARKS

Claims 31-57, as amended, are pending in this application for the Examiner's review and consideration. Claim 31 was amended to include a proviso that excludes specific compounds disclosed in FR 2,387,956; P. Sharan *et. al., J. Indian Chem. Soc.* 66:6, 393-94 (1989); N.K. Sangwan *et al., J. Prakt. Chem.*, 330:1, 137-141 (1988); and V.K. Ahluwalia *et al., Indian J. Chem., Sect. B* 27:B(1), 70-71 (1988). Claims 48, 49, and 56 were amended to be written in independent form. As no new matter has been added herein, these changes should be entered.

Applicant believes the application is in condition for allowance and earnestly requests allowance thereof. If the Examiner has any questions or suggestions to expedite allowance of this application, however, the Examiner is respectfully invited to call the undersigned to discuss the matter further.

A fee of $84 is believed to be due for the addition of one (1) independent claim in excess of three (3). Please charge this and any other required fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date

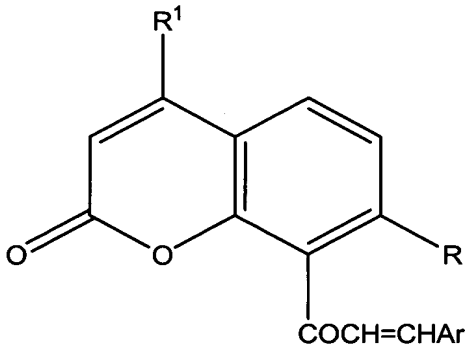
Paul E. Dietze (Reg. No. 45,627)
For: Thomas G. Rowan (Reg. No. 34,419)
PENNIE & EDMONDS LLP
1667 K Street, N.W.
Washington, DC 20006

(202) 496-4400

Appendix A

Changes to the Claims

31. (Amended) A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents: a substituted or unsubstituted, aromatic or non-aromatic, carbocyclic or heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the carbocyclic or heterocyclic group may be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, and (l) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents OH, OR^{10} or $OCOR^{11}$ wherein R^{10} and R^{11} are as defined above; and R^1 represents H or a C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3;

with the proviso that:

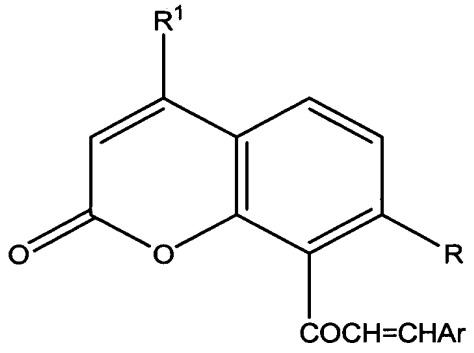
(i) when R^1 is CH_3 and Ris OH, then Ar cannot be 4-pyridyl, 4-methylphenyl, 3-nitrophenyl, 3-methoxy-4-ethoxyphenyl, 3-methoxy-4-n-butoxyphenyl, 4-(N,N-dimethylamino)phenyl, 2-hydroxy-3,5-dibromophenyl, 2-hydroxy-5-methylphenyl, 4-chlorophenyl, phenyl, 3-methoxyphenyl,4-methoxyphenyl,or 3,4-dimethoxyphenyl;

(ii) when R^1 is CH_3 and R is $OCOCH_3$, the group, then Ar cannot be phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-(N,N-dimethylamino)phenyl, 3-methoxy-4-acetoxyphenyl, 3,4,5-trimethoxyphenyl, or 2-chlorophenyl;

(iii) when R^1 is phenyl or H and R is OCH_3 or OH, then Ar cannot be 4-methoxyphenyl; and

(iv) when R^1 is CH_3 and R is OCH_3 or OH, then Ar cannot be 4-methoxyphenyl or 3,4-dimethoxyphenyl.

48. (Amended) A method of treating cancer in a patient comprising administering to the patient a compound of formula: [claim 31]



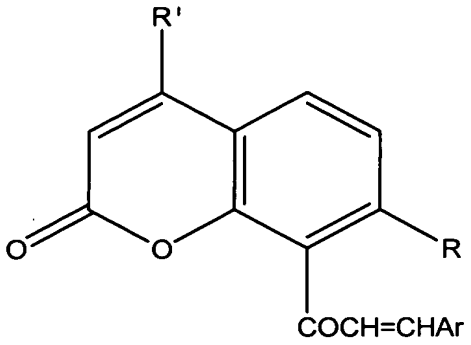
or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents: a substituted or unsubstituted, aromatic or non-aromatic, carbocyclic or heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the carbocyclic or heterocyclic group may be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, and (l) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents OH, OR^{10} or $OCOR^{11}$ wherein R^{10} and R^{11} are as defined above; and

R^1 represents H or a C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

49. (Amended) A method of treating or preventing neoplasms in a patient comprising administering to the patient a compound of [claim 31] formula



(I)

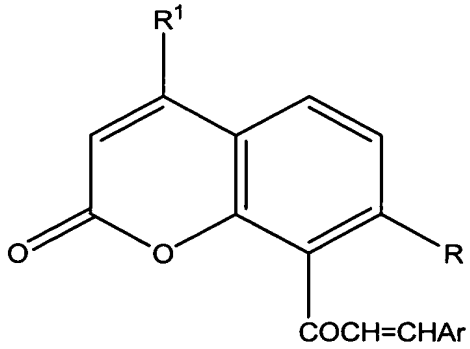
or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents: a substituted or unsubstituted, aromatic or non-aromatic, carbocyclic or heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the carbocyclic or heterocyclic group may be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, and (l) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents OH, OR^{10} or $OCOR^{11}$ wherein R^{10} and R^{11} are as defined above; and R^1 represents H or a C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

56. (Amended) A [The] pharmaceutical composition [of claim 55 further] comprising :

(A) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents: a substituted or unsubstituted, aromatic or non-aromatic, carbocyclic or heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the carbocyclic or heterocyclic group may be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, and (l) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

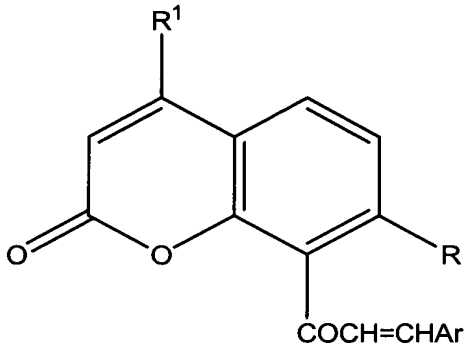
R represents OH, OR^{10} or $OCOR^{11}$ wherein R^{10} and R^{11} are as defined above; and R^1 represents H or a C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3; and

(B) one or more antineoplastic agents.

Appendix B

Currently Pending Claims

31. (Amended) A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents: a substituted or unsubstituted, aromatic or non-aromatic, carbocyclic or heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the carbocyclic or heterocyclic group may be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, and (I) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents OH, OR^{10} or $OCOR^{11}$ wherein R^{10} and R^{11} are as defined above; and R^1 represents H or a C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3;

with the proviso that:

(i) when R^1 is CH_3 and Ris OH, then Ar cannot be 4-pyridyl, 4-methylphenyl, 3-nitrophenyl, 3-methoxy-4-ethoxyphenyl, 3-methoxy-4-n-butoxyphenyl, 4-(N,N-dimethylamino)phenyl, 2-hydroxy-3,5-dibromophenyl, 2-hydroxy-5-methylphenyl, 4-chlorophenyl, phenyl, 3-methoxyphenyl,4-methoxyphenyl,or 3,4-dimethoxyphenyl;

(ii) when R^1 is CH_3 and R is $OCOCH_3$, the group, then Ar cannot be phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-(N,N-dimethylamino)phenyl, 3-methoxy-4-acetoxyphenyl, 3,4,5-trimethoxyphenyl, or 2-chlorophenyl;

(iii) when R^1 is phenyl or H and R is OCH_3 or OH, then Ar cannot be 4-methoxyphenyl; and

(iv) when R^1 is CH_3 and R is OCH_3 or OH, then Ar cannot be 4-methoxyphenyl or 3,4-dimethoxyphenyl.

32. The compound of claim 31, wherein Ar represents a substituted or unsubstituted, aromatic or non-aromatic, heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the heterocyclic group can be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturate C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from: Cl, Br, F, OMe, NO_2 and, and (l) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group.

33. The compound of claim 31, wherein the Ar group is a heterocyclic group, wherein at least one of the ring atoms is a nitrogen atom.

34. The compound of claim 33, wherein Ar represents pyridyl or indolyl.

35. The compound of claim 31, wherein Ar represents a substituted or unsubstituted, aromatic or non-aromatic carbocyclic group.

36. The compound of claim 31, wherein the substituents on the Ar group are selected from the group consisting of: $NHCOCH_3$, $N(R^8)(R^8)$, OR^{10},and $-OC0R^{11}$.

37. The compound of claim 31, wherein Ar is substituted with one or more OR^{10} groups and R^{10} is a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group.

38. The compound of claim 37, wherein R^{10} is methyl.

39. The compound of claim 37, wherein Ar is a phenyl or a phenyl substituted with from 1 to 3 methoxy groups.

40. The compound of claim 31, wherein R is an unsaturated C_{1-6} straight or branched hydrocarbyl group.

41. The compound of claim 40, wherein R is $OCH=C(CH_3)_2$, $OCH_2CMe=CH_2$, $OCH_2CH=CH_2$, or $OCH_2C\equiv CH$.

42. The compound of claim 31, wherein Ar is selected from phenyl, trimethoxyphenyl, 3-pyridyl, 4-pyridyl, and 3-indolyl; and R is selected from $OCH=C(CH_3)_2$, $OCH_2CMe=CH_2$, $OCH_2CH=CH_2$ or $OCH_2C\equiv CH$.

43. The compound of claim 35, wherein

Ar is selected from phenyl, which may be unsubstituted or substituted with from 1 to 3 substituents independently selected from Cl, Br, F, OMe, NO_2, CF_3, C_{1-4} alkyl, NMe_2, NEt_2, SCH_3, and $NHCOCH_3$; thienyl; 2-furyl; 3-pyridyl; 4-pyridyl; or indolyl; and

R is selected from OH or OCH_2R^1, wherein R_1 is selected from $-CH=CMe_2$, $-CMe=CH_2$, $-CH=CH_2$ and $-C\equiv CH$.

44. The compound of claim 31, wherein R^6 and R^8 are the same or different and each is independently H or C_{1-4} alkyl.

45. The compound of claim 31, wherein R^{10} and R^{11} are each independently a saturated or unsaturated C_{1-6} straight chain or branched hydrocarbyl group.

46. The compound of claim 45, wherein R^{10} and R^{11} are selected from methyl, ethyl, n-propyl, and isopropyl.

47. The compound of claim 31, selected from the group consisting of:

1-[4-methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-(pyridine-3-yl)propen-1-one;

1-[4-methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-phenylpropen-1-one;

1-[4-methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-(3,4,5-trimethoxyphenyl)-propen-1-one;

1-[4-methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(pyridine-3-yl)propen-1-one;

1-[4-methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-phenylpropen-1-one;

1-[4-methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(3-methoxyphenyl)propen-1-one;

1-[4-methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(3,4,5-trimethoxyphenyI)propen-1-one;

1-[4-methyl-7-(allyloxy)coumarin-8-yl]-3-phenylpropen-1-one;

1-[4-methyl-7-(allyloxy)coumarin-8-yl]-3-(pyridin-3-yl)propen-1-one;

1-[4-methyl-7-(allyloxy)coumarin-8-yl]-3-(3-methoxyphenyl)propen-1-one;

1-[4-methyl-7-(allyloxy)coumarin-3-yl]-3-(3, 4 ,5-trimethoxyphenyl)propen-1-one;

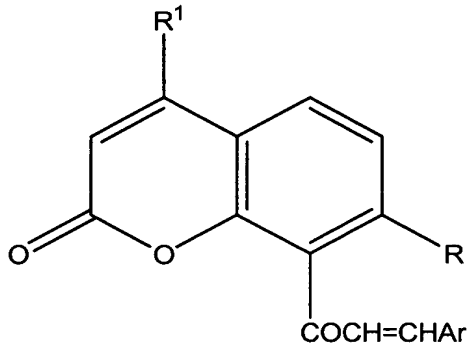
1-[4-methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(3, 4, 5-trimethoxyphenyl)propen-1-one;

1 -[4-methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-phenylpropen-1-one;

1 -[4-methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(pyridin-3-yl)propen-1-one; and

1 -[4-methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(3-methoxyphenyl)propen-1-one.

48. (Amended) A method of treating cancer in a patient comprising administering to the patient a compound of formula:

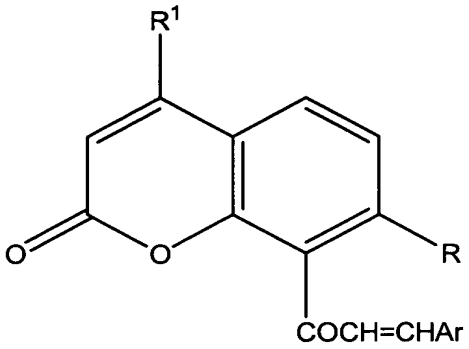


or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents: a substituted or unsubstituted, aromatic or non-aromatic, carbocyclic or heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the carbocyclic or heterocyclic group may be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, and (l) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents OH, OR^{10} or $OCOR^{11}$ wherein R^{10} and R^{11} are as defined above; and R^1 represents H or a C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

49. (Amended) A method of treating or preventing neoplasms in a patient comprising administering to the patient a compound of formula:



or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents: a substituted or unsubstituted, aromatic or non-aromatic, carbocyclic or heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the carbocyclic or heterocyclic group may be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, and (l) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents OH, OR^{10} or $OCOR^{11}$ wherein R^{10} and R^{11} are as defined above; and R^1 represents H or a C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

50. The method of claim 49, wherein the neoplasms are located in the uterus, ovary, or breast.

51. The method of claim 48, wherein the cancer is a paclitaxel or docetaxel resistant cancer.

52. The method of claim 48, further comprising administering one or more antineoplastic agents.

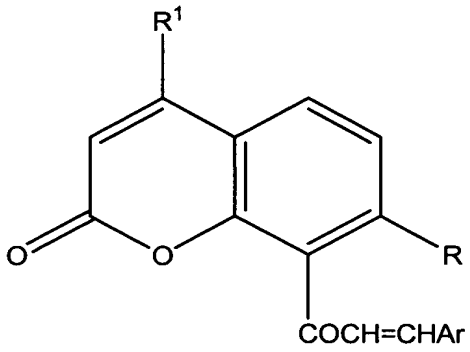
53. The method of claim 52, wherein antineoplastic agent comprises paclitaxel or docetaxel.

54. A method of treating or preventing menopausal disorders and osteoporosis in a patient comprising administering to the patient a compound of claim 31.

55. A pharmaceutical composition comprising a compound of claim 31 and a pharmaceutically acceptable excipient.

56. (Amended) A [The] pharmaceutical composition comprising:

(A) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents: a substituted or unsubstituted, aromatic or non-aromatic, carbocyclic or heterocyclic group having from 5 to 10 ring atoms or two rings with each ring containing 5 or 6 ring atoms, wherein the heterocyclic group comprises a heteroatom selected from N, O and S, and wherein the carbocyclic or heterocyclic group may be unsubstituted or substituted with one or more substituents selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} alkyl, (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3, and (l) $-OCOR^{11}$ wherein R^{11} represents a saturated or unsaturated C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents OH, OR^{10} or $OCOR^{11}$ wherein R^{10} and R^{11} are as defined above; and

R^1 represents H or a C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted with from 1 to 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3; and

(B) one or more antineoplastic agents.

57. The pharmaceutical composition of claim 56, wherein the antineoplastic agent is selected from paclitaxel or docetaxel.